Outcome and treatment of nocardiosis after solid organ transplantation: new insights from a European study

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40-word summary: In our study of 117 organ-transplant recipients with nocardiosis, a history of tumor, invasive fungal infection, donor age and no acute rejection were independently associated with one-year mortality. Short-course antibiotic treatment (≤120 days), used in 17 patients, appeared promising.

Running title: Outcome of nocardiosis after SOT

Members of the European Study Group for *Nocardia* in Solid Organ Transplantation:

Individual collaborators and scientific groups who are members of the European Study Group for *Nocardia* in Solid Organ Transplantation are listed in the Supplementary data or in the author list.

ABSTRACT

Background: Solid organ transplant (SOT) recipients are at risk of nocardiosis, a rare opportunistic bacterial infection, but prognosis and outcome of these patients are poorly defined. Our objectives were to identify factors associated with one-year mortality after nocardiosis and describe the outcome of patients receiving short-course antibiotics (≤120 days).

Methods: We analyzed data from a multicenter European case-control study that included 117 SOT recipients with nocardiosis diagnosed between 2000 and 2014. Factors associated with one-year all-cause mortality were identified using multivariable conditional logistic regression.

Results: One-year mortality was 10-fold higher in patients with nocardiosis (16.2%, 19/117) than in control transplant recipients (1.3%, 3/233, p<0.001). A history of tumor (odds ratio [OR] 1.4; 95% confidence interval [CI] 1.1-1.8), invasive fungal infection in the six months before nocardiosis (OR 1.3; 95%CI 1.1-1.5) and donor age (OR 1.0046; 95%CI 1.0007-1.0083) were independently associated with one-year mortality. Acute rejection in the year before nocardiosis was associated with improved survival (OR 0.85; 95%CI 0.73-0.98). Seventeen patients received short-course antibiotics (median duration 56 [24-120] days) with a one-year success rate (cured and surviving) of 88% and a 5.9% risk of relapse (median follow-up 49 [6-136] month).

Conclusions: One-year mortality was 10-fold higher in SOT patients with nocardiosis than in those without. Four factors, largely reflecting general medical condition rather than severity and/or management of nocardiosis, were independently associated with one-year mortality. Patients receiving short-course antibiotic treatment had good outcomes, suggesting this may be a strategy for further study.

Keywords: *Nocardia*, mortality, organ transplantation, prognosis, opportunistic infections

LIST OF ABBREVIATIONS

16S rRNA:	16S ribosomal ribonucleic acid
95% CI:	95% confidence interval
ATG:	antithymocyte globulin
CCI:	Charlson comorbidity index
CMV:	cytomegalovirus
CNS:	central nervous system
CRP:	C-reactive protein
NS:	not significant
OFN:	Observatoire Français des Nocardioses
OR:	odds ratio
SOT:	solid organ transplantation
spp.:	species
SXT:	trimethoprim–sulfamethoxazole (cotrimoxazole)

INTRODUCTION

Nocardia spp. is a filamentous environmental Gram-positive bacterium that causes infection in immunocompromised patients, such as solid organ transplantation (SOT) recipients [1]. Because inhalation is the main portal of entry for *Nocardia*, lung involvement is frequent and bacteria may subsequently spread to other organs, such as the brain [1].

Although several reports have indicated that nocardiosis is associated with increased mortality in SOT recipients, a precise assessment of its impact on outcome is still lacking [2]. Indeed, reported post-SOT nocardiosis mortality rates vary from 0 to 70%, depending on the characteristics of the studied populations and durations of follow-up [3-8]. Furthermore, prognostic factors have not been precisely identified, because only limited-size retrospective studies have been published. Of note, a univariate analysis performed in a study of 31 patients with nocardiosis (including nine transplant recipients) suggested that dissemination and presence of brain abscesses were associated with increased mortality [9].

Theoretically, factors that could influence the outcome of nocardiosis include its presentation (e.g., presence of cerebral abscesses [9]), possible co-infections with other opportunistic pathogens (e.g., *Aspergillus* and cytomegalovirus [CMV] [6]), therapeutic modalities (e.g., appropriateness of antibiotics according to species identification and antimicrobial susceptibility testing [2]), occurrence of adverse effects associated with antibiotics (e.g., toxicity of trimethoprim–sulfamethoxazole [SXT] [6, 10, 11]) and presence of co-morbidities [12]. Improved understanding of the impact of nocardiosis on outcomes after SOT and of factors associated with outcomes may help delineate a group of patients requiring a specific initial diagnostic work-up, treatment and/or follow-up.

Another challenge in the field of post-SOT nocardiosis is the optimal duration of antibiotic treatment with regard to the risk of relapse on the one hand and to the adverse effects and costs of these agents on the other. Current recommendations suggest at least six months of antimicrobial therapy for pulmonary or soft tissue infections and a minimum of 9-12 months for brain abscess [13]. These guidelines are based on a retrospective study of 25 pulmonary cases published in 1982 that described a high rate of relapse (60%, 3/5 patients) among patients who received SXT alone for less than four months [14]. Strikingly, a more recent study that included 12 heart transplant recipients suggested that a shorter (≤120 days) treatment course was feasible in pulmonary nocardiosis, without relapse [15].

We recently reported the results of a multicenter case-control study conducted to identify risk factors for nocardiosis [16]. In the present study, our primary objective was to identify factors associated with all-cause mortality one year after diagnosis of nocardiosis in the SOT population. Our secondary objective was to assess the risk of relapse associated with short-course (≤120 days) antibiotic treatment for *Nocardia* infection.

MATERIAL AND METHODS

Study design and participants

In our previously published retrospective case-control study, 351 SOT recipients (117 patients with post-transplant nocardiosis and 234 matched control transplant recipients, details of whom can be found elsewhere [16]) were included from 36 hospitals in Western Europe (participating centers are listed in the Appendix and in the author list) [16]. The present study includes the same 351 patients. Patients with nocardiosis were included if they met all the following criteria: (1) SOT recipient; (2) isolation of *Nocardia spp*. in a clinical sample after transplant; (3) signs and/or symptoms suggestive of nocardiosis; (4) diagnosis made between January 2000 and December 2014. To avoid selection bias, cases were identified in each institution using systematic and comprehensive screening of local microbiological, pathology and transplantation databases.

Variables

Data were collected from the patients' medical records by local investigators using dedicated case-report forms. The date of diagnosis was defined as the day on which the first clinical sample (e.g., sputum) that allowed identification of *Nocardia* spp. was collected. Variables potentially associated with patient outcome were divided into three groups:

(1) Collected patient characteristics included: age, sex, comorbidities at time of nocardiosis (Charlson Comorbidity Index (CCI), **Supplementary Table 1**) [17], transplant details (history of previous transplant, donor age, type of donation (deceased vs. living), organ transplanted), immunosuppressive regimen used, history of acute allograft rejection and history of opportunistic infections (CMV infection and/or disease as defined elsewhere [18], CMV serostatus at time of transplantation, bloodstream infection and history of treated proven or probable invasive fungal infection in the six months before nocardiosis). High-dose corticosteroids were defined as >20 mg/day of prednisone for at least one month or >2 pulses of 500 mg of intravenous methylprednisolone. High calcineurin inhibitor trough levels were defined as >10 ng/mL for tacrolimus and >300 ng/mL for cyclosporine.

(2) Factors related to the characteristics of nocardiosis included: time from transplant to nocardiosis, time between occurrence of symptoms and diagnosis, sites of infection, eventual dissemination (defined as the involvement of at least two non-contiguous organs and/or positive blood cultures), biological blood values at

the time of *Nocardia* infection (kidney function, C-reactive protein, leukocytes, neutrophils, lymphocytes), additional pathogens (identification of at least one other microbial pathogen at the time of *Nocardia* diagnosis), *Nocardia* species, susceptibility to SXT.

(3) Factors associated with the treatment of nocardiosis included the antimicrobial agents used, appropriateness of the antimicrobial agents prescribed in the first two weeks of therapy in the initial regimen (appropriateness being defined as the administration of antibiotics with *in vitro* activity against the infecting strain [19]), use of bactericidal antibiotics (amikacin, carbapenems, third-generation cephalosporin restricted to ceftriaxone and cefotaxime [20]) in the first two weeks of treatment, occurrence of antibiotic-related adverse effects and need for surgery due to nocardiosis. Total duration of antibiotic treatment was recorded and a short-course was defined as ≤120 days [15].

Relapse was defined as the association of clinical and radiological signs of nocardiosis with isolation of the same *Nocardia* species found at initial diagnosis, after the cessation of antimicrobial treatment for nocardiosis. Determination of nocardiosis as the cause of death was based on physician analysis of the medical chart.

Microbiology

To identify the species of each *Nocardia* strain, amplification and sequencing of a fragment of the gene coding for the 16S ribosomal RNA (16S rRNA) or *hsp65* genes were mandatory, as described previously [16]. Ideally, antibiotic susceptibility testing was performed by determination of the minimal inhibitory concentration (MIC) in broth microdilution [21] but MICs evaluated by E-test® strips or antibiotic disk diffusion on agar plates were considered acceptable when performed by a trained microbiologist [22-25]. When antibiotic susceptibility testing was missing, stored strains were *a posteriori* sent to the French expert laboratory for nocardiosis (Observatoire Français des Nocardioses, Lyon, France) to perform the missing tests.

Statistical methods

Final analysis was conducted after all data had been recorded and verified. Continuous data are presented as median (range) or mean (± standard deviation), as appropriate. Categorical data are presented as numbers and percentage of total. The primary outcome was survival 12 months after diagnosis of *Nocardia* infection. Survival was assessed using Kaplan-Meier curves and compared between groups using log-rank tests. Univariate analyses were performed using Fisher's exact test or chi-square test, as appropriate, to compare

categorical variables, and Student t-tests were performed to compare continuous variables. A bilateral p-value <0.05 was considered as statistically significant. Variables with a p-value <0.2 on univariate analysis were included in the final multivariable conditional logistic regression analysis. All statistical analyses were performed using R Statistical software (version 3.2.0; R Foundation for Statistical Computing, Vienna, Austria).

Ethical aspects

As previously described, this work was approved by local ethics committees and fulfilled the regulatory standards of each participating country [16].

RESULTS

Participants and overall mortality

One hundred and seventeen SOT recipients with nocardiosis were included from 36 European institutions; full case descriptions can be found elsewhere [16]. The median duration of follow-up from the date of nocardiosis diagnosis was 45.3 [0.1-151.9] months. One-year all-cause mortality was significantly higher in patients with nocardiosis (16.2%, 19/117) than in control transplant patients (1.3%, 3/233) ($p<0.001$) (**Figure 1A**). In the nocardiosis non-survivors, death occurred after a median of 134 [4-359] days post-infection. Nocardiosis was listed as the cause of death in 52.6% of the non-survivors (10/19); when comparing deaths related or not to nocardiosis, there was no statistically significant difference in the length of time between nocardiosis and death (100 [19-302] days vs. 149 [4-359] days, $p=0.57$).

Prognostic factors

In univariate analysis (**Table 1**), one-year mortality was significantly higher in patients with an additional pathogen at the time of diagnosis of nocardiosis, invasive fungal infection in the six months before nocardiosis, older donor age and longer time from transplantation to nocardiosis (all $p<0.05$). No therapeutic variables were associated with survival at one year. In multivariable analysis (**Table 2**), history of tumor (defined as a non-metastatic tumor [if active or initially treated in the 5 years before diagnosis of nocardiosis] or metastatic solid tumor), invasive fungal infection in the six months before nocardiosis and older donor age were independently associated with increased one-year mortality. Conversely, acute rejection in the year before nocardiosis was associated with a better survival. Survival analyses are shown in **Figures 1B to D**.

Description of initial management

During the first two weeks of treatment, appropriate antibiotics were prescribed in 94.6% of the patients (105/111) based on results of antibiotic susceptibility testing (**Supplementary Tables 2 and 3**). Bactericidal antibiotics were used as initial therapy in 66/109 of the patients (60.6%) and two simultaneous appropriate antibiotics in 48/111 (43.2%). At least one antibiotic-attributed adverse effect was reported in 46.6% of the patients (54/116), affecting the bone marrow (n=24), kidneys (n=22), digestive system (n=11) and/or skin (n=5). Twenty-three patients required surgery (23/117, 19.7%).

Risk of relapse and short-course antibiotic treatment

Twenty-seven patients (23.0%) received short-course antibiotic treatment. However, the impact of antibiotic duration on the risk of relapse could only be assessed in 17 patients, as death occurred within 120 days in 10 of these patients (37.0%). These 10 patients died while still receiving active antimicrobial therapy against *Nocardia* and half of these deaths (5/10) were directly attributed to nocardiosis. A detailed description of the 17 analyzable patients is provided in **Table 3;** the median duration of antibiotic treatment was 56 [24-120] days**.** Compared with the entire cohort, the 17 patients in whom antibiotics were deliberately given for ≤120 days were less likely to have disseminated disease (2/17 [11.8%] vs. 50/117 [42.7%], p<0.01) and tended to less frequently have CNS infection (1/17 [5.9%] vs. 30/117 [25.6%], p=0.12). After a median follow-up of 49 [6-136] months, 15 of the 17 patients were cured (88.2%, including 2/2 with disseminated infection, 1/1 with CNS infection and 11/12 with lung infection), one died within the first year (5.9%) and one relapsed (5.9%). The patient who died had *Candida* bloodstream infection at the time of diagnosis. Among the 15 patients who did not relapse despite administration of short-course antibiotics, all received appropriate initial antibiotics (15/15, 100%) but the percentages of patients who received bactericidal antibiotics (7/15, 46.7%) or an association of two appropriate antibiotics (5/15, 33.3%) in the first two weeks of treatment were not significantly different to those observed in the entire cohort (p=0.46 and p=0.65 respectively). After cessation of therapy, secondary prophylaxis with SXT was given to 62.5% (10/16) of the patients who had received short-course antibiotics.

Seven patients (7/117, 6.0%) had a relapse during follow-up. These patients had a median duration of treatment of 165 [51-501] days with one patient receiving short-course treatment (51 days). This patient, who had isolated lung infection, had relapsing nocardiosis despite the use of appropriate and bactericidal antibiotics in the first two weeks of treatment. Among the 7 patients who relapsed, a single one died within one year, due to an episode of acute allograft rejection.

Among 98 survivors at one year, 92 (93.9%) had no relapse after a median follow-up of 4.3 [1-12.6] years. Among these survivors, the median duration of treatment was 195 [24-1981] days. Duration of antibiotic treatment was significantly longer in patients with disseminated or CNS nocardiosis (**Supplementary Figure 1).**

In the 8/117 patients who had an infection limited to the skin and soft-tissues (6.8%), the median duration of antibiotic treatment was 103 [35-351] days and 6 of these patients (75.0%) required surgery. Cure was

achieved in 7 patients (87.5%, including 4 patients with short-course antibiotics) and one patient (12.5%) relapsed 137 days after the end of therapy (which included >4 months of antibiotics and no surgery).

DISCUSSION

In our European cohort, one-year all-cause mortality was more than ten-times higher in the 117 SOT recipients with nocardiosis than in control transplant recipients. Four factors were independently associated with risk of death one year after nocardiosis: a history of tumor, invasive fungal infection in the 6 months before nocardiosis, donor age and absence of acute organ rejection in the year before nocardiosis.

The mortality rate observed in our study (16.2%, 19/117) is comparable to that in a previous study reporting on 35 patients with post-SOT nocardiosis (6-month mortality=14.3%, 5/35) [6] but appears to be lower than in other reports (~30%) [4, 5]. This apparent discrepancy may be explained by the different outcome periods used in the various studies and the large proportion of lung recipients in the two latter studies. Higher mortality rates have been reported in patients with fungal opportunistic infections after SOT, including pneumocystosis (90-day mortality 23.1%, 6/26) [26], aspergillosis (12-week mortality, 39.3%, 44/112) [27] and mucormycosis (90-day mortality 58.2%, 57/105) [27]. We were, therefore, not surprised to observe that occurrence of an invasive fungal infection in the 6 months prior to nocardiosis (reported in 17.0% of our cohort and in 37.5% of the patients who died) was independently associated with an increased risk of death, as has been suggested previously [8].

Other patient characteristics were also independently associated with death after nocardiosis. First, we observed that a history of tumor was an independent prognostic factor after nocardiosis. Second, donor age was independently associated with one-year mortality, an observation that is in agreement with data from the French transplantation agency (Agence de la Biomédecine) reporting that donor age was associated with reduced graft and recipient survival after heart, lung, liver and kidney transplantation [28].

Of interest, we observed significantly lower mortality among patients who experienced an acute rejection episode in the year before nocardiosis. Although this observation may appear surprising, these patients tended to have received higher doses of corticosteroids in the six months before diagnosis and to more frequently have a high calcineurin inhibitor level, suggesting that although a higher degree of immunosuppression may increase the risk of post-SOT nocardiosis, it is associated with a better outcome [16]. This association may be explained by the fact that patients with a high degree of immunosuppression are more closely monitored and promptly investigated in case of fever or respiratory symptoms leading to earlier diagnosis, but one can also

hypothesize that a greater inflammatory response may be associated with a worse prognosis in *Nocardia* infection.

Strikingly, no therapeutic variable was associated with patient survival. Because of the non-interventional design of our study, we cannot rule out a beneficial effect of the early use of appropriate antibiotics, or the impact of using antibiotic combinations or bactericidal versus bacteriostatic antibiotics. Expert recommendations regarding the initial choice of antibiotics [13] should therefore be followed, initially using antibiotics active against a broad spectrum of *Nocardia* species, such as SXT, amikacin, third-generation cephalosporins (restricted to ceftriaxone and cefotaxime), carbapenem (restricted to imipenem and meropenem) or linezolid. Antibiotic combinations that include bactericidal antibiotics should be considered for severe cases, including CNS nocardiosis. Treatment should be adapted as soon as possible to molecular biology-based species identification and results of antimicrobial susceptibility testing.

A somewhat controversial finding when considering current recommendations is our data regarding the duration of treatment for nocardiosis. Guidelines propose at least a six-month antibiotic course for nocardiosis, but few data are available to support this statement. In 1982, Wallace and co-workers reported 25 cases of pulmonary nocardiosis (in patients without SOT) and described a higher rate of relapse among patients receiving less than four months of treatment [14]. Almost thirty years later, in a retrospective description of 12 cases of nocardiosis after heart transplantation who received short-course (≤120 days) antibiotic treatment, Tripodi *et al* [15] reported that none of their patients who were treated with 3-4 weeks of intravenous bactericidal antibiotics followed by 1-3 months of oral antibiotic relapsed. Reducing antibiotic treatment duration could have potential benefits, such as cost-savings and reduction in the risk of adverse events, especially among transplant recipients. Indeed, 46.5% of our patients experienced at least one drug-related adverse effect. Among 17 analyzable patients (including only two with disseminated infection and one with CNS infection) receiving short-course antibiotic treatment frequently followed by secondary prophylaxis with SXT, we observed an 88.2% cure rate without relapse, one nocardiosis-independent death and one relapse. Our results should be interpreted with caution because of the risk of selection bias associated with the non-randomized design but, together with the findings of Tripodi *et al* [15], support the need for a randomized controlled trial on the duration of antibiotic treatment for nocardiosis. Such a study should take into account important factors that were not available in our study (e.g., dosing of antibiotics, potential reduction or tapering of immunosuppressive drugs, patient compliance). However, the relatively low number of events

(<20% deaths at one year and rare relapses) observed in our study and the rarity of nocardiosis after SOT would make such a trial difficult to perform.

Once therapy is stopped, the role of secondary prophylaxis using low-dose SXT has not yet been determined. Secondary prophylaxis with SXT was prescribed to 62.5% (10/16) of our patients receiving short-course antibiotic treatment, which may explain the low incidence of relapse. However, we and others have shown previously that the low doses of SXT used to prevent pneumocystosis after SOT are not effective as primary prophylaxis against nocardiosis [16]. Because such prophylaxis is usually well tolerated and also prevents other opportunistic infections, we would recommend its use at higher dosage (800 mg sulfamethoxazole per day) as secondary prophylaxis.

Our study has several limitations, including its retrospective design, lack of data regarding reduction or tapering of immunosuppressive drugs or compliance to therapy, and the fact that antibiotic dose adjustment to body weight or kidney function was not taken into account. The limited size of our study and its design may explain the absence of a significant association between the severity of nocardiosis (e.g., presence of brain abscess) and mortality [9]. Antibiotic susceptibility testing was not standardized with only 40% of the bacterial strains sent to the French expert laboratory and most tests were performed by antibiotic disk diffusion on agar plates. However, although disk diffusion is not considered a gold-standard by the CLSI, it has been shown to have a high percentage agreement with reference methods [21, 22].

In conclusion, we provide the first assessment of factors associated with one-year mortality after post-SOT nocardiosis. Our findings support the suggestion that short-course antibiotic treatment may be a strategy for further study.

NOTES

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this article.

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Figure 1. **One-year survival curves after diagnosis of post-solid organ transplantation nocardiosis.** Survival was assessed using Kaplan-Meier curves and compared among groups using log-rank tests. **A.** Survival curves of patients with nocardiosis (n=117) and matched control transplant recipients (n=234). **B to D.** Survival curves among patients with nocardiosis according to the presence of invasive fungal infection (including *Pneumocystis* pneumonia) in the 6 months before nocardiosis (**B**)**,** history of tumor defined as a non-metastatic tumor (if active or initially treated in the 5 years before diagnosis of nocardiosis) or metastatic solid tumor (**C**) and episode of acute rejection in the year before nocardiosis (**D**).

Table 1. **Factors associated with one-year all-cause mortality in univariate analysis among the 117 patients with post-solid organ transplantation nocardiosis.**

Characteristics	Dead at 1 year n=19	Alive at 1 year n=98	p-value
Clinical characteristics			
Age at diagnosis (years) (mean ± SD)	61.4 (12.3)	54.5 (13.5)	0.07
Male (n, %)	14 (73.7)	60 (61.2)	0.44
Charlson comorbidity index† at diagnosis n=112 (mean, SD)	4.13 (1.7)	3.71 (1.8)	0.34
History of tumor ‡ n=112	3 (18.8)	5 (5.2)	0.08
Transplantation characteristics			
History of previous transplant	1 (5.2)	17 (17.3)	0.30
Donor age (mean ± SD) n=110	54.5 (15.8)	46.0 (16.8)	**0.044**
Deceased donor (vs living)	18 (94.7)	89 (90.8)	1
Non-thoracic (pancreas, liver, kidney) organ	12 (63.2)	66 (67.3)	0.79
Immunosuppressive regimen and rejection data			
Cyclosporine A at diagnosis	4 (21.1)	17 (17.3)	0.75
Tacrolimus at diagnosis	15 (78.9)	78 (80.0)	1
High CNI level in the month before *Nocardia* infection	5 (26.3)	46 (46.9)	0.16
Use of antiproliferative agents (AZA or MMF) at diagnosis	14 (73.7)	81 (82.7)	0.35
Corticosteroids at diagnosis (mg*) (mean ± SD) n=115	7.0 (4.0)	9.1 (7.2)	0.12
Acute rejection episode in the year before diagnosis n=116	2 (10.5)	30 (30.6)	0.09
Acute rejection episode in the six months before diagnosis n=116	1 (5.3)	24 (24.5)	0.07
High-dose steroids in the six months before diagnosis n=116	1 (5.3)	19 (19.4)	0.19
Plasma exchange in the six months before diagnosis n=116	0 (0)	5 (5.1)	0.59
Depleting antibodies (ATG or Rituximab) in the six months before diagnosis** n=116	0 (0)	6 (6.1)	0.59
SXT prophylaxis at diagnosis	2 (10.5)	19 (19.4)	0.52
Associated infectious diseases			
CMV infection in the six months before diagnosis	3 (15.8)	14 (14.3)	1
CMV disease in the six months before diagnosis	2 (10.5)	3 (3.1)	0.19
CMV serostatus			0.67

Low risk: D-R-	5 (26.3)	17 (17.3)	
Intermediate risk: D-R+ or D+R+	10 (52.6)	50 (51.0)	
High risk: D+R-	4 (21.1)	27 (27.6)	
Bloodstream infection in the six months before diagnosis	1 (5.3)	5 (5.1)	1
Additional pathogen[$] at diagnosis	12 (63.2)	28 (28.6)	**< 0.01**
Fungal infection[#] in the six months before diagnosis n=112	6 (37.5)	13 (13.5)	**0.029**
Biological characteristics			
Glomerular filtration rate ¶ (ml/min/1.73m^2) at diagnosis (mean, SD) n=115	41.4 (24.3)	50.1 (27.6)	0.19
WBC count at diagnosis (x1000/mm^3) (mean, SD) n=115	11.3 (5.8)	11.5 (6.7)	0.88
Neutrophil count at diagnosis (x1000/mm^3) (mean, SD) n=105	9.5 (5.6)	9.8 (6.7)	0.98
Lymphocyte count at diagnosis (x1000/mm^3) (mean, SD) n=105	0.6 (0.4)	0.8 (0.6)	0.35
C-reactive protein at diagnosis (mg/L) (mean, SD) n=109	91.8 (67.5)	128.4 (90.9)	0.13
Nocardiosis characteristics and treatment			
Time from transplantation to diagnosis (days) (mean, SD)	1611.7 (1692.7)	976.2 (1277.7)	**0.046**
Time from symptoms to diagnosis (days) (mean, SD) n=114	19.4 (18.4)	25.9 (24.1)	0.21
Disseminated infection	9 (47.4)	41 (41.8)	0.85
Lung or pleural involvement	16 (84.2)	85 (86.7)	0.72
Central nervous system involvement	8 (42.1)	22 (22.4)	0.13
Skin and soft-tissue involvement	5 (26.3)	32 (32.7)	0.78
Bloodstream infection	2 (10.5)	7 (7.1)	0.64
***Nocardia* species**			0.33
N. farcinica	8 (42.1)	33 (33.7)	
N.* non-*farcinica	11 (57.9)	65 (66.3)	
Strain susceptible to SXT n=113	14 (73.7)	85 (86.7)	0.44
Appropriate antibiotics[$] during the first two weeks of treatment n=111	15 (88.2)	90 (95.7)	0.23
Administration of carbapenems, 3GC, amikacin or SXT during the first two weeks of treatment n=113	15 (83.3)	89 (93.7)	0.15
Bactericidal antibiotic (carbapenems, 3GC, amikacin) during the first two weeks of treatment n=109	10 (62.5)	56 (60.2)	1
Association of two appropriate antibiotics during the first two weeks of treatment n=111	7 (41.2)	41 (43.6)	1

Antibiotic-related adverse effects n=116	9 (47.4)	45 (46.4)	1
Need for surgery	4 (21.1)	19 (19.4)	1

NOTE. 3GC: Third-generation cephalosporin (restricted to ceftriaxone and cefotaxime); ATG: antithymocyte globulin; AZA: azathioprine; CMV: cytomegalovirus; CNI: calcineurin inhibitor; diagnosis: date of the diagnosis of nocardiosis; MMF: mycophenolate mofetil; n: number of data analyzed (when <117); PCP: *Pneumocystis* pneumonia; SD: standard deviation; SXT: trimethoprim–sulfamethoxazole; WBC: white blood cell. Data are n (%) unless otherwise indicated.

†Apart from "history of tumor", none of the other individual variables of the Charlson comorbidity index were associated with one-year mortality, with p-values > 0.2. ‡ defined as a non-metastatic tumor (if active or initially treated in the 5 years before diagnosis of nocardiosis) (n=7) or metastatic solid tumor (n=1). *All the corticosteroid doses are expressed in milligrams (mg) of methylprednisolone equivalent per day. **In the 6 months before diagnosis of *Nocardia* infection, none of our patients received other types of lymphocyte-depleting or modulating antibodies. ¶As estimated by MDRD formula. [$]Fifty-one additional microbial pathogens were identified at time of nocardiosis among forty patients: 19 fungi, 11 CMV, 8 Gram-negative bacteria, 4 Gram-positive bacteria, 3 *C. difficile*, 2 *Legionella* spp., 1 HHV8, 2 other viruses and 1 *Toxoplasma gondii.* [#]19 patients experienced at least one invasive fungal infection (10 aspergillosis, 3 mucormycosis, 3 invasive candidiasis, 2 *Alternaria* spp., 1 *Fusarium* spp., 1 *Scedosporium* spp., 1 *Pneumocystis*). [$]Appropriate antibiotic is defined as a drug with demonstrated *in vitro* activity against the isolated *Nocardia* strain.

Table 2. Factors associated with one-year all-cause mortality after multivariable conditional logistic regression analysis among 117 patients with nocardiosis after solid organ transplantation.

Characteristics	OR [95%IC]	p-value
History of tumor *	1.4 [1.1- 1.8]	0.02
Fungal infection† in the 6 months before diagnosis	1.3 [1.1-1.5]	< 0.01
Donor age (per year)	1.0046 [1.0007-1.0083]	0.02
Acute rejection episode in the year before diagnosis	0.85 [0.73-0.98]	0.03

NOTE. *defined as a non-metastatic tumor (if active or initially treated in the 5 years before diagnosis of nocardiosis) (n=7) or metastatic solid tumor (n=1). † 19 patients experienced at least one invasive fungal infection (10 aspergillosis, 3 mucormycosis, 3 invasive candidiasis, 2 *Alternaria* spp., 1 *Fusarium* spp., 1 *Scedosporium* spp., 1 *Pneumocystis*).

Table 3. Description of patients with post-solid organ transplantation nocardiosis receiving short-course antibiotic treatment (≤ 120 days)

Patient	Age at time of diagnosis	Lung involvement †	Disseminated infection	CNS infection	Skin and soft-tissue	Type of positive sample	*Nocardia* species	Antibiotic treatment duration (days)	Outcome at one year	Secondary prophylaxis with SXT, dose‡, duration*	Length of follow-up (months)
1	52	Multilobar, bilateral	No	No	No	Sputum, bronchial aspirate, BAL and pleural fluid	ND	42	Alive, no relapse	Yes, 2800, till death	41
2	67	None	No	No	Yes	Abscess fluid	*N. farcinica*	90	Alive, no relapse	Yes, 5600, 6m	49
3	50	Unilobar, unilateral	Yes	No	No	Bronchial aspirate, BAL and blood	*N. nova* complex	47	Alive, no relapse	Yes, 2400, 12m	48
4	63	Multilobar, bilateral	No	No	No	Sputum	*N. farcinica*	24	Alive, no relapse	Yes, 1600, ND	132
5	36	Multilobar, bilateral	No	No	No	Sputum	*N. abscessus*	51	Relapse, alive at one year	Yes, 1600, ND	26
6	56	Multilobar, bilateral	No	No	No	Bronchial aspirate and BAL	*N. nova complex*	39	Alive, no relapse	Yes, 1200, ND	62
7	65	Multilobar, unilateral	No	No	No	Bronchial aspirate and BAL	*N. farcinica*	76	Alive, no relapse	Yes, 2400, 4m	22
8	69	Multilobar, bilateral	No	No	No	Bronchial aspirate and BAL	*N. farcinica*	70	Alive, no relapse	No	63
9	80	None	No	No	Yes	Skin biopsy	*N. flavorosea*	56	Alive no relapse	No	27
10	71	None	No	No	Yes	Abscess fluid	*N. farcinica*	102	Dead, no relapse*	Yes, 5600, 5m	6
11	30	Unilobar, unilateral	No	No	No	BAL	*N. farcinica*	45	Alive, no relapse	No	23
12	60	Multilobar, bilateral	No	No	No	BAL	*N. farcinica*	33	Alive at one year, no relapse	Yes, 2400, till death	136

13	32	None	No	No	Yes	Skin biopsy	*N. abscessus*	90	Alive at one year, no relapse	No	72
14	60	Unilobar, unilateral	Yes	Yes	Yes	Abscess fluid	*N. cerradoensis*	47	Alive at one year, no relapse	Yes, 2400, till death	15
15	40	Multilobar, bilateral	No	No	No	Pleural fluid	ND	90	Alive at one year, no relapse	No	133
16	67	None	No	No	Yes	Skin biopsy	*N. anaemiae*	105	Alive at one year, no relapse	No	86
17	56	Unilobar, unilateral	No	No	No	Sputum and BAL	ND	120	Alive at one year, no relapse	ND	90

NOTE. † Lung involvement was assessed with lung CT-scan (CT) for all patients except patients 1 and 9. ‡ dose was expressed as sulfamethoxazole weekly dose in milligrams. * Death unrelated to nocardiosis. BAL: bronchoalveolar lavage, CNS: central nervous system, m: months, ND: not determined, SXT: trimethoprim–sulfamethoxazole.

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